REMARKS

Upon entry of this amendment, claims 1, 3, 14-25, 27, 38, and 42-50 and will be pending in the application. Claims 43-50 are added as supported in the specification, for example, at paragraphs [0022] and [0023] and Example 3. Claims 2, 4-13, 26, 28-37, and 39-41 have been canceled. Claim 3 is amended to correct its dependency. No new matter is introduced by this amendment.

I. Claims 1, 3, 15, 27, 38, and 42 are patentable over Nicolaides 1.

Claims 1, 3, 15, 27, 38, and 42 are rejected under 35 U.S.C. § 103 for alleged obviousness over Nicolaides 1 (United States Published Application 2002/0068284). Applicants respectfully request reconsideration and withdrawal of the rejection because there are elements of the claimed invention that the cited reference neither teaches nor suggests.

Nicolaides 1 fails to teach or suggest the generation of a bacterium resistant to a plurality of antibiotics. Nicolaides 1 describes a cell expressing a dominant negative mismatch repair (MMR) gene as having an altered mismatch control pathway, which thereby alters a gene or set of genes controlling a *single* phenotype. (Nicolaides 1, [0058].) In other words, Nicolaides 1 describes a hypermutable bacterium having one or more mutations resulting in any *one* of a number of altered phenotypes, such as resistance to an antibiotic (*e.g.*, kanamycin) (Nicolaides 1, [0058]), heat resistance, or high recombinant protein production (Nicolaides 1, Example 3).

Reliance on the description of Nicolaides 1 of hypermutable bacteria that may be used to "screen for novel mutations in a gene or a set of genes that produce variant siblings that exhibit a new output trait(s) not found in the wild-type cells" as the motivation of that reference to screen for bacteria having multi-antibiotic resistance is misplaced. The new output traits to which that passage refers are found in differing cell siblings. This is further evidenced, for example, by the description of paragraph [0017] of Nicolaides 1 wherein an embodiment of the invention described therein is a method for generating an MMR-proficient bacterium with a new output trait and by Examples 2 and 3. There is simply no teaching or suggestion in the description of Nicolaides 1 of a single cell exhibiting resistance to multiple antibiotics.

Given this deficiency, the rejection of claims for alleged obviousness under section 103(a) should be withdrawn. *In re Payne*, 203 U.S.P.Q. 245, 255 (C.C.P.A. 1979) (references relied upon to support rejection under section 103 must place the claimed invention in the possession of the public); *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974) (all limitations set forth in a patent claim must be taught or suggested in the prior art to establish a *prima facie* case of obviousness). Withdrawal of the rejection is thus respectfully requested.

II. Claims 1, 19, 27, and 38 are patentable over Iris in view of Stemmer, Johnston, Aronshtam, LeClerc, Drummond, Moreland, and Morris.

Claims 1, 19, 27, and 38 are rejected under 35 U.S.C. § 103 for alleged obviousness over U.S. Patent No. 6,221,585 to Iris *et al.* ("Iris") in view of U.S. Published Application 2002/0049104 to Stemmer *et al.* ("Stemmer"), U.S. Patent No. 6,043,048 to Johnston *et al.* ("Johnston"), Aronshtam and Marinus (*Nuc. Acids Res.*, 24(13):2498-2504 (1996)) ("Aronshtam"), LeClerc *et al.* (*Science*, 274:1208-1211 (1996)) ("LeClerc"), Drummond *et al.* (*J. Biol. Chem.*, 271(33):19645-19648 (1996)) ("Drummond"), Moreland *et al.* (*Cancer Res.*, 59:2102-2104 (1999)) ("Moreland"), and Morris *et al.* (*J. Infect. Dis.*, 171:954-960 (1995)) ("Morris"). Applicants respectfully request reconsideration and withdrawal of the rejection.

When applying 35 U.S.C. § 103, adherence to the following tenets of patent law is required: (a) the claimed invention must be considered as a whole; (b) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (c) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (d) reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 U.S.P.Q. 182, 187 n.5 (Fed. Cir. 1986); MPEP § 2141.

No motivation to combine the cited references to generate bacteria having multiantibiotic resistance has been established.

It is asserted that the Johnston reference suggests that multiantibiotic resistant bacteria can be generated by culturing cells in a medium containing two or more antibiotics. Applicants respectfully disagree with this characterization of the Johnston reference.

Johnston describes the very limited circumstance of multiantibiotic resistance wherein bacterial beta-lactamases are induced by a beta-lactam antibiotic and subsequently challenged with an indicator antibiotic, thereby preventing false susceptibility results to the indicator antibiotic. Culturing of the bacterial cells in the indicator antibiotic does not induce bacterial resistance thereto. Thus, it would not be obvious to one of ordinary skill in the art to generate multiantibiotic-resistant bacteria simply by culturing the bacteria in medium containing two or more antibiotics.

The LeClerc, Drummond, and Moreland references are alleged by the Office Action to show that "those in the art were aware of the fact that defective mismatch repair has been known to result in mutations leading to cellular resistance to drugs." (Office Action at page 4.) A prior art reference, however, must be considered in its entirety. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). The Drummond and Moreland references describe the necessity of mismatch repair proteins in linking chemotherapeutic agent-induced DNA damage to cell death. As each of the references describes mechanisms for inhibiting the replicative bypass of DNA lesions induced by chemotherapeutic agents in an effort to overcome the effect of defective mismatch repair in cancer cells (*e.g.*, the Drummond reference describes the introduction of a dominant negative p53 gene into cisplatin-resistant cells to increase resistance to the agent; the Moreland reference describes the use of aphidicolin to increase sensitivity to methylating agents), one of ordinary skill in the art would not have been motivated to consider the Drummond or Moreland reference in combination with the other cited references in an effort to *create* hypermutable cells. Similarly, the aim of the LeClerc reference is to identify pre-existing mutator strains with a goal of identifying a mechanism to *prevent* such mutation. For example, the LeClerc reference suggests an antisense strategy for preventing a mutator phenotype. (LeClerc at page 1210.) Likewise, the Morris reference describes multidrug resistance of *M. tuberculosis* mediated by an accumulation of mutations in genes encoding drug targets. The Morris reference, however, does not teach, suggest, or motivate one of ordinary skill in the art to *generate* bacteria having multiantibiotic resistance. Rather, the aim of the Morris reference is to identify and prevent such resistance. One of ordinary skill in the art thus would not have considered the Drummond, Moreland, LeClerc, or Morris reference in combination with the

other cited references in seeking to develop a method for *creating* multi-antibiotic resistant bacteria.

The Aronshtam reference describes increased Lac- to Lac+ reversion associated with dominant mutations in a MutL gene induced by hydroxylamine-treatment of cells. (Aronshtam at page 2501.) The mutagenicity associated with dominant negative mutations of mismatch repair genes induces random mutations throughout the host's genome. Stemmer, however, teaches away from approaches wherein the entire genetic background is the subject of selection because "deleterious effects often counterbalance the desirable effects, reducing the overall success and efficiency of the program." (Stemmer, [0080].) Stemmer thus manipulates genetic elements in a synchronized manner to exert control over a phenotype. (Stemmer, [0084].) One having ordinary skill in the art would not have been motivated to combine Stemmer with Aronshtam. For the same reason, the ordinarily skilled artisan would not have been motivated to combine LeClerc, Drummond, or Moreland, each of which also describes cells having a mutable phenotype as a result of a mismatch repair defect, with Stemmer.

In addition, the Stemmer and Iris references propose two wholly different methods for identifying genes associated with a phenotype. The methods of the Stemmer reference rely on generation of genetic diversity of chimeric nucleotide sequences. In the Stemmer method, members of a library of diverse conjoint polynucleotides are introduced into a host cell for expression and selection. (Stemmer, [0054].) Vectors conferring a desired phenotype are recovered and subjected to diversification until an optimized set of elements are identified. (Stemmer, Figures 3 and 4.) Thus, the method of Stemmer begins with a nucleic acid molecule having an unknown function and derives the phenotype associated therewith. In contrast, the Iris reference first identifies a phenotype of interest and then compares a *homogeneous* population of nucleic acid molecules from a population having the phenotype of interest to a second *homogeneous* population of nucleic acid molecules not having the phenotype of interest. (Iris, Col. 8.) Mismatched duplex nucleic acid molecules between the first and second populations purportedly contain the genes that confer the phenotype of interest. In short, the methods of Iris and Stemmer are completely contrasting approaches to identifying genes associated with a phenotype which the ordinarily skilled artisan would not have been motivated to combine.

The present Office Action acknowledges the differences between the modes of operation of the methods of the Stemmer and Iris references but asserts that "these references are not cited to combine their teachings with reference to the modes of operation, but to demonstrate that those in the art would look to the differences in genetic makeup with reference to target phenotypes as a basis for the development of disease therapies." (Office Action at page 3.) A prior art reference, however, must be considered in its entirety. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). "It is impermissible within the framework of Section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *In re Wesslau*, 147 U.S.P.Q. 391, 393 (C.C.P.A. 1965).

Applicants respectfully assert that the requisite motivation to combine the cited references to arrive at the present invention has not been established and that the references themselves teach away from such combination.

The cited references fail to teach introduction of a dominant negative allele of a mismatch repair gene.

Applicants respectfully submit that the Iris, Stemmer, Johnston, and Aronshtam references fail to teach or suggest introduction of a dominant negative allele of a mismatch repair gene to yield multiple antibiotic resistance as presently claimed. The Iris reference nowhere mentions how the organism exhibiting the phenotype of interest – antibiotic resistance - is generated. Stemmer suggests diversification of conjoint constructs by employing site-directed mutagenesis in mismatch repair-deficient host organisms. (Stemmer, [0113] and [0119].) However, Stemmer does not teach or suggest the introduction of a dominant negative allele of a mismatch repair gene to induce phenotypic variation. See Carter *et al.*, *Nuc. Acids Res.*, 13(12):4431-4443 (1985), a copy of which is submitted herewith, which is cited in paragraph [0119] of Stemmer. The Aronshtam reference describes increased Lac- to Lac+ reversion associated with dominant mutations in a MutL gene induced by hydroxylamine treatment of cells. (Aronshtam at page 2501.)

LeClerc, Drummond, Moreland, and Morris fail to remedy this deficiency. As discussed above, none of those references teach or suggest introduction of a dominant negative allele of a mismatch repair gene into bacteria to create multiantibiotic-resistant microbes. Indeed, as previously explained, each of those references teaches away from the present invention.

Moreover, none of the cited references teaches or suggests stabilization of the hypermutable bacteria. Applicants emphatically deny the assertion on page 5 of the Office Action that Applicants previously noted a rational and scientific argument as to the obviousness of such a step had been provided. Applicants again request that such an assertion be properly supported. 37 C.F.R. § 1.104(d). Absent such support, Applicants maintain that it would ***not*** have been obvious to one of ordinary skill in the art to make the antibiotic resistant bacteria genetically stable. Deficiencies of the cited references cannot be remedied by general conclusions about what is "basic knowledge" or "common sense." *In re Lee*, 277 F.3d at 1344-45.

In short, Applicants assert that a *prima facie* case of obviousness of claims 1, 19, 27, and 38 has not been established on this record. Reconsideration and withdrawal of the rejection is respectfully requested.

III. Claims 1, 3, 27, 38, and 42 are patentable over Iris in view of Stemmer, Johnston, and either of Nicolaides 2 or Nicolaides 3, further in view of LeClerc, Drummond, Moreland, and Morris.

Claims 1, 3, 27, 38, and 42 are rejected for alleged obviousness over Iris in view of Stemmer, Johnston, and either of Nicolaides 2 (Nicolaides *et al.*, *Mol. Cell. Biol.*, 18(3):1635-1641 (1998)) or Nicolaides 3 (U.S. Patent No., 6,146,894), further in view of LeClerc, Drummond, Moreland, and Morris. Applicants traverse the rejection.

The above remarks regarding the lack of obviousness of claims 1, 19, 27, and 38 in view of the Iris, Stemmer, Johnston, LeClerc, Drummond, Moreland, and Morris references are equally applicable to the present rejection. The LeClerc, Drummond, Moreland, and Morris references fail to teach or suggest *generation* of a hypermutable organism by introducing a dominant negative allele of a mismatch repair gene. Indeed, as previously

explained, each of the references teaches away from generating a cell of the invention. The Stemmer and Iris references also fail to teach or suggest generation of a hypermutable organism by introducing a dominant negative allele of a mismatch repair gene.

Nicolaides 2 or Nicolaides 3 cannot be relied upon to remedy the deficiencies of the cited references. Nicolaides 2 and Nicolaides 3 describe introduction of a dominant negative allele of a mismatch repair gene into a cell to make it hypermutable. One of ordinary skill in the art would not have combined LeClerc, Drummond, or Moreland with Nicolaides 2 or Nicolaides 3. The Drummond and Moreland references describe the necessity of mismatch repair proteins in linking chemotherapeutic agent-induced DNA damage to cell death. As each of the references describes mechanisms for inhibiting the replicative bypass of DNA lesions induced by chemotherapeutic agents in an effort to overcome the effect of defective mismatch repair in cancer cells (*e.g.*, the Drummond reference describes the introduction of a dominant negative p53 gene into cisplatin-resistant cells to increase resistance to the agent; the Moreland reference describes the use of aphidicolin to increase sensitivity to methylating agents), one of ordinary skill in the art would not have been motivated to consider the Drummond or Moreland reference in combination with Nicolaides 2 or Nicolaides 3 in an effort to *create* hypermutable cells. Similarly, the aim of the LeClerc reference is to identify pre-existing mutator strains with a goal of identifying a mechanism to *prevent* such mutation. For example, the LeClerc reference suggests an antisense strategy for preventing a mutator phenotype. (LeClerc at page 1210.) Likewise, the Morris reference describes multidrug resistance of *M. tuberculosis* mediated by an accumulation of mutations in genes encoding drug targets. The Morris reference, however, does not teach, suggest, or motivate one of ordinary skill in the art to *generate* bacteria having multiantibiotic resistance. Rather, the aim of the Morris reference is to identify and prevent such resistance. One of ordinary skill in the art thus would not have considered the Drummond, Moreland, LeClerc, or Morris reference in combination with Nicolaides 2 or Nicolaides 3 in seeking to develop a method for *creating* multi-antibiotic resistant bacteria.

Stemmer also teaches away from combination with an approach wherein the entire genetic background is the subject of selection because "deleterious effects often counterbalance the desirable effects, reducing the overall success and efficiency of the program." (Stemmer, [0080].) One having ordinary skill in the art thus would not be

motivated to combine the Stemmer disclosure with the teaching of either of Nicolaides 2 or Nicolaides 3.

In short, Applicants assert that a *prima facie* case of obviousness of claims 1, 3, 27, 38, and 42 has not been established on this record. Reconsideration and withdrawal of the rejection is respectfully requested.

IV. Claims 1, 3, 14-25, 27, 38, and 42 are patentable over either of (A) Iris, Stemmer, Johnston, and Aronshtam or (B) Iris, Stemmer, Johnston, either of Nicolaides 2 or 3, LeClerc, Drummond, Moreland, Morris, Lin, Chang, Setterstrom, and The Merck Index.

Claims 1, 3, 14-25, 27, 38, and 42 are rejected for alleged obviousness over either of (A) Iris, Stemmer, Johnston, and Aronshtam or (B) Iris, Stemmer, Johnston, either of Nicolaides 2 or 3, LeClerc, Drummond, Moreland, Morris, U.S. Patent No. 6,025,400 to Lin ("Lin"), U.S. Patent No. 6,043,220 to Chang *et al.* ("Chang"), U.S. Patent No. 6,410,056 to Setterstrom *et al.* ("Setterstrom"), and The Merck Index (1983, pages 2036, 5032-5033, and 6448-6449). Applicants respectfully disagree with the rejection.

The above remarks regarding the lack of obviousness of claims 1, 19, 27, and 38 in view of the Iris, Stemmer, Aronshtam, Johnston, LeClerc, Drummond, Moreland, and Morris references are equally applicable to the present rejection. Additionally, the above remarks regarding the lack of obviousness of claims 1, 3, 27, 38, and 42 in view of the Iris, Stemmer, Johnston, Nicolaides 2 or Nicolaides 3, LeClerc, Drummond, Moreland, and Morris references are equally applicable to the present rejection.

Furthermore, bacterial resistance to a plurality of antibiotics including those listed in claims 14-25 has not been established. The Lin, Chang, and Setterstrom references and The Merck Index are relied upon for the alleged showing that the antibiotics of claims 14-25 were known in the art. However, no motivation to combine those references with any of Iris, Stemmer, Aronshtam, Johnston, Nicolaides 2 or Nicolaides 3, LeClerc, Drummond, Moreland, and Morris or a reasonable expectation of success in generating resistance to the antibiotics identified by introducing a dominant negative allele of a mismatch repair gene into bacteria has been established on the present record. Absent these elements, a *prima facie*

case of obviousness of claims 1, 3, 14-25, 27, 38, and 42 cannot be demonstrated. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, the undersigned may be contacted at 215-557-5908.

Respectfully submitted,

Date: January 6, 2005

Felicity E. Groth
Registration No. 47,042

Enclosures:
Supplemental Information Disclosure Statement
Carter *et al., Nuc. Acids Res.*, 13(12):4431-4443 (1985)
Request for Continued Examination
Request for Extension of Time

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439